

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) EP 0 992 495 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
12.04.2000 Bulletin 2000/15

(21) Application number: 98920547.1

(22) Date of filing: 25.05.1998

(51) Int. Cl.⁷: C07D 217/26

(86) International application number:
PCT/ES98/00145

(87) International publication number:
WO 98/54149 (03.12.1998 Gazette 1998/48)

(84) Designated Contracting States:
AT BE CH DE DK FR GB IE IT LI NL PT SE

(30) Priority: 29.05.1997 ES 9701169

(71) Applicant: ESTEVE QUIMICA, S.A.
08024 Barcelona (ES)

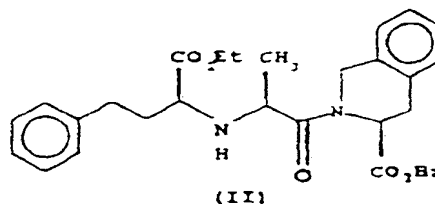
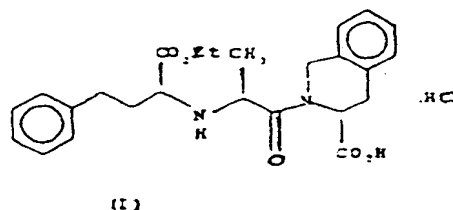
(72) Inventors:
• MONSALVATJE LLAGOSTERA, Montserrat
E-08024 Barcelona (ES)

• BARTRA SANMART, Martí
E-08024 Barcelona (ES)
• TOMAS NAVARRO, Jaime
E-08024 Barcelona (ES)
• PUIG TORRES, Salvador
E-08024 Barcelona (ES)

(74) Representative:
Carpintero Lopez, Francisco
HERRERO & ASOCIADOS, S.L.
Alcalá, 21
28014 Madrid (ES)

(54) **PROCESS FOR OBTAINING QUINAPRYL HYDROCHLORIDE AND SOLVATES USEFUL FOR ISOLATING AND PURIFYING QUINAPRYL HYDROCHLORIDE**

(57) The process for obtaining quinapril hydrochloride (I) comprises the stages of: a) hydrogenolysis of the benzyl ester of quinapril (II) by treatment in an alcoholic solvent, with concentrated hydrochloric acid or a solution of hydrogen chloride in isopropanol, and hydrogenation; b) removal of the solvent; c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate; d) treatment of said solvate with a Class 3 solvent which forms a solvate of quinapril hydrochloride from which it can be removed by drying without degrading; and e) drying of the solvate from step d) to yield quinapril hydrochloride (I), an antihypertensive agent.



EP 0 992 495 A1

Description

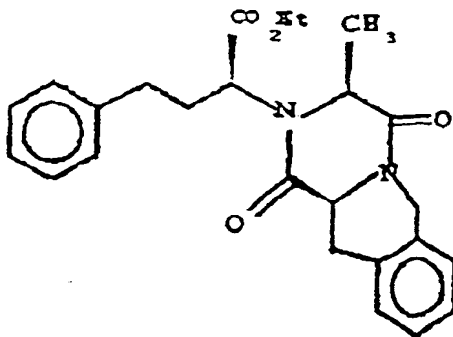
FIELD OF THE INVENTION

[0001] This invention refers to a procedure for obtaining quinapril hydrochloride, as well as new solvates of quinapril hydrochloride, obtained by the use of Class 3 solvents, from which it is possible to eliminate the solvent by drying without degradation of the product, and which are useful for the isolation and purification of quinapril hydrochloride. The process can be developed at the industrial scale.

BACKGROUND OF THE INVENTION

[0002] Quinapril is the common international denomination of the chemical compound named (S)-2- [(S)-N- [(S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid. Quinapril and its pharmaceutically acceptable salts are antihypertensive agents which act as angiotensin converting enzyme (ACE) inhibitors.

[0003] The first description of quinapril appears in the United States Patent No. US 4.344.949, which also describes its preparation starting from the ethyl ester of (S,S)- α -[(1-carboxyethyl)amino]phenylbutanoic acid and from the benzyl or t-butyl ester of (S)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid by peptide condensation with dicyclohexylcarbodiimide (DCC) and activation with hydroxibenzotriazole. The benzyl or t-butyl ester of quinapril so obtained is unprotected by catalytic hydrogenation or by treatment with trifluoroacetic acid, being the final isolation of quinapril carried out (at the laboratory scale) by precipitation with ethyl ether and by lyophilization of an aqueous solution. The isolation of quinapril is a very delicate procedure, as this product degrades very easily by intramolecular cyclisation to yield a diketopiperazine of formula



both in aqueous or organic solution as in the solid state.

[0004] The process described in said patent US 4.344.949 presents the drawbacks which are typical of the use of DCC, as the condensations carried out in the presence of DCC yield a fair amount of impurities, with the subsequent reduction in the yield (61%), thus the resulting dicyclohexylurea must be separated and, additionally, the carbodiimides are responsible for very severe allergies.

[0005] Quinapril hydrochloride is the salt which is usually employed in the manufacture medicinal products which contain quinapril.

[0006] The United States Patent No. 4.761.479 mentions that obtaining and purifying quinapril hydrochloride is hindered by its ease in degrading into by-products, essentially the diketopiperazine shown before. Said US patent No. 4.761.479 describes a process for obtaining quinapril hydrochloride which comprises unprotecting the t-butyl ester of quinapril with HCl gas in acetic acid, the isolation of the precipitation product after the addition of xylene and vacuum distillation, and the purification of the quinapril hydrochloride by crystallisation with acetonitrile to yield a crystalline solvate of acetonitrile. The solvent of said solvate can be removed, without degradation of the quinapril hydrochloride, by drying in a vacuum oven. However, acetonitrile is a Class 2 solvent, defined by the ICH [International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use] as a "Non-mutagenic carcinogen in animals or possible cause of other irreversible toxicity such as neurotoxicity, teratogenesis or suspect of significant reversible toxicity, and, therefore, its proportion has to be limited". In the case of acetonitrile, the ICH recommends a limit not above 250 ppm (0.025%). This limit is difficult to achieve at the industrial scale due to the little stability of the product.

[0007] The Belgian Patent No. BE 892.552 describes another process for the preparation of quinapril hydrochloride

starting from (S,S)- α - [(1- carboxyethyl) amino] phenylbutanoic acid by activation with 1,1'-carbonyldiimidazole, which yields an N-carboxyanhydride which reacts *in situ*, without prior isolation, with the benzyl ester of (S)-1,2,3,4- tetrahydro-3-isoquinolinecarboxylic acid to yield the corresponding benzyl ester of quinapril with a yield of 56%. The resulting quinapril, protected in the form of a benzyl ester, is subsequently hydrogenated in the presence of Pd/C and it is treated with hydrochloric acid to give the quinapril hydrochloride, which is purified by chromatography and lyophilization, at a very low yield (37%). This synthetic route is also mentioned in a generic manner in the Spanish Patent ES 2.004.804, but without giving any specific conditions, nor yields, nor a description of the properties of the products obtained. Specifically, the synthesis of quinapril hydrochloride is not exemplified at all.

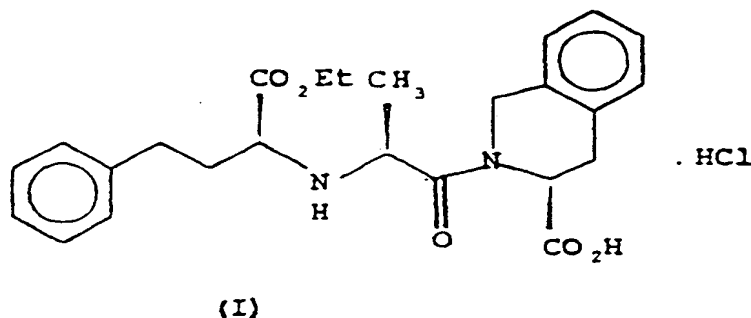
[0008] In general, all the processes described for obtaining quinapril hydrochloride are characterised by their difficulty or by their low yields. Only the US Patent US 4.761.479 describes a process for the industrial isolation and purification of quinapril hydrochloride, starting from the t-butyl ester of quinapril. However, said procedure has the disadvantage of using a carcinogenic solvent (acetonitrile) to obtain the corresponding solvate.

[0009] Consequently, there is a need to have a process for obtaining and purifying quinapril hydrochloride, which may be carried out at the industrial scale, and which overcomes the previously mentioned drawbacks. In order to obtain and purify quinapril hydrochloride at a high yield, the invention proposes the precipitation of said product in the form of a toluene solvate. Therefore, one of the objects of the invention is constituted by a process for obtaining quinapril hydrochloride, which comprises its isolation as the toluene solvate.

[0010] On the other hand, the solvates of quinapril hydrochloride, which are useful compounds for the purification of said product, are, in general, products from which it is extremely difficult to remove the solvent without partially degrading the quinapril hydrochloride. The only known solvate of quinapril hydrochloride which can be dried without degradation of the product is the acetonitrile solvate, but said solvate has been obtained with a carcinogenic solvent. In order to overcome these drawbacks, the invention provides solvates of quinapril hydrochloride which can be dried to remove the solvent without degrading the quinapril hydrochloride, and which have been obtained by the use of non-carcinogenic solvents. Therefore, an additional object of the invention is constituted by new solvates of quinapril hydrochloride, of solvents belonging to Class 3, from which it is possible to remove the solvent by drying without degradation of quinapril hydrochloride. Class 3 solvents are defined, according to the ICH, as "Solvents with a low toxic potential to man, not being it necessary to establish an exposure limit based on health criteria. Class 3 solvents have a ADE (Allowable Daily Exposure) equal or greater than 50 mg per day".

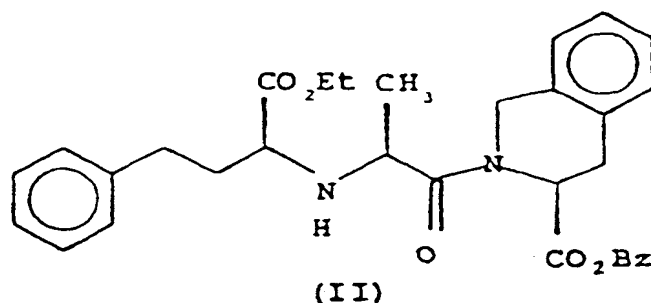
DETAILED DESCRIPTION OF THE INVENTION

[0011] The invention provides a process for obtaining quinapril hydrochloride of formula (I)



which comprises the stages of:

a) hydrogenolysis of the benzyl ester of quinapril (II)



where Bz is the benzyl radical;

b) removal of the solvent used in step a);

c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate;

d) treatment of the toluene solvate of quinapril hydrochloride with a solvent belonging to Class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying in an oven without degrading the quinapril hydrochloride; and

e) drying of the solvate obtained in step d) to yield quinapril hydrochloride (I).

[0012] The benzyl ester of quinapril (II) is a known product which can be obtained by whichever of the processes described in the patents US 4,344,949 and BE 892,552, mentioned earlier, as well as in the patents EP 135181 and EP 135182 where it is described, in a general manner, the obtaining of the protected quinapril in the form of the benzyl ester starting from (S,S)- α - [(1- carboxyethyl) amino] phenylbutanoic acid, by activation with alkenephosphonic anhydrides.

[0013] The hydrogenolysis of the benzyl ester of quinapril (II) can be carried out in an alcoholic solvent, such as ethanol or isopropanol, with concentrated hydrochloric acid or with a solution of hydrogen chloride in isopropanol, hydrogenation with hydrogen gas at a pressure comprised between approximately 10^4 Pa (0,1 bar) and approximately 2×10^5 Pa (2 bar), at a temperature comprised between 10 and 40 °C, in the presence of a suitable hydrogenation catalyst, for instance, Pd/C.

[0014] In a specific embodiment, the hydrogenolysis reaction is carried out using ethanol as a solvent, concentrated hydrochloric acid, a pressure of 10^5 Pa (1 bar) and room temperature. In another specific embodiment, the hydrogenolysis reaction is carried out using isopropanol as a solvent, a solution of hydrogen chloride in isopropanol, a pressure of 2×10^5 Pa (2 bar) and a temperature of approximately 30 °C.

[0015] The molar ratio between the benzyl ester of quinapril (II) and hydrochloric acid can be equal or slightly greater to the stoichiometric one, although preferably said molar ratio is stoichiometric as, in the event of a large defect of hydrochloric acid, quinapril tends to cyclise to form the diketopiperazine shown above, while in the event of an excess of acid, decomposition of the quinapril hydrochloride, and of the benzyl ester of quinapril itself, takes place.

[0016] Generally, hydrochloric acid is added at room temperature, and the reaction between the hydrochloric acid and the benzyl ester of quinapril (II) is virtually immediate, within minutes.

[0017] Because the solution of the benzyl ester of quinapril hydrochloride in isopropanol is more stable than the solution of the free base and, on the other hand, considering the instability of the benzyl ester of quinapril (II), the most reliable manner of preserving such product for short periods of time is maintaining it as the hydrochloride in solution in isopropanol.

[0018] Once hydrogenation is finalised, the catalyst is removed, for example, by filtration, and the solvent employed, ethanol or isopropanol, is removed, for instance, by vacuum distillation, at a temperature below 40 °C, as at greater temperatures cyclisation of the product to form the diketopiperazine is quantitatively more significant, and toluene is added. These operations involving the removal of the solvent and addition of toluene can be repeated a variable number of times. Subsequently, the bulk of the reaction is allowed to stand at room temperature for the quinapril hydrochloride to precipitate in the form of the toluene solvate.

[0019] In a specific embodiment, for the obtaining of the toluene solvate of quinapril hydrochloride starting from the raw solution in the solvent used (ethanol or isopropanol), said solution is distilled down to a defined volume of approximately 1.6 ml/g of benzyl ester of quinapril and subsequently, an amount of toluene of approximately 2,25 ml of toluene per gram of benzyl ester of quinapril is added. After this, distillation is carried out again to the same volume as before, and the same amount of toluene is added. By working under these conditions, quinapril hydrochloride precipitates in the form of the toluene solvate within a period of time comprised between 20 and 60 minutes. By following this precip-

itation process for the toluene solvate, using isopropanol as a solvent, a greater yield is obtained than by employing ethanol, which can largely be accounted for by the fact that quinapril hydrochloride is more soluble in ethanol than in isopropanol.

[0020] The toluene solvate of precipitated quinapril hydrochloride is filtered and dried, and a yield comprised between approximately 85% and 90% is obtained. This solvate is a very suitable intermediate for the subsequent purification of quinapril hydrochloride according to the process proposed by the present invention. The spectroscopic characteristics (IR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$) of this toluene solvate are contained in Example 2.1. The attempts made to remove the toluene by drying of said solvate, without degrading the quinapril hydrochloride, were unsuccessful.

[0021] Subsequently, the toluene solvate of quinapril hydrochloride is treated with a solvent belonging to Class 3, i.e., non-toxic, non-carcinogenic, for example, ethyl formate or methyl acetate, at a temperature comprised between 40 °C and 45 °C, for a period of time comprised between 1 and 2 hours, and it is next cooled down to a temperature comprised between 20 °C and 25 °C, for a period of time comprised between 1 and 2 hours, to form the corresponding solvate, either of ethyl formate or of methyl acetate, which is then filtered and dried, with a yield in any of the cases of approximately 95%. These solvates can be dried in an oven, to remove the solvent, without degrading the quinapril hydrochloride. These solvates are key intermediates for obtaining quinapril hydrochloride of a high degree of purity (99.8%) according to the process object of this invention. The spectroscopic (IR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$) and X-Ray diffraction characteristics of these solvates are contained in Examples 2.2. and 2.3.

[0022] The drying of the ethyl formate or of the methyl acetate solvates of quinapril hydrochloride obtained in this manner, in order to yield quinapril hydrochloride, can be carried out in an oven, for example in a vacuum oven, at a temperature comprised between approximately 40 and 50 °C, for a period of time comprised between 12 and 24 hours, depending on the amount of solvate to be dried. The resulting quinapril hydrochloride, the spectroscopic (IR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$), optical rotation and X-Ray diffraction characteristics of which are collected in example 2.4., is an amorphous product, the X-ray diffraction pattern of which exhibits few peaks and with a low intensity, and consequently, *a priori*, it is an amorphous product.

[0023] The hydrogenation of the product resulting after the addition of hydrochloric acid or of the solution of hydrogen chloride in isopropanol in step a) can be carried out without prior isolation of the intermediate formed. Equally, the bulk of the reaction resulting from the hydrogenolysis can be subjected to distillation in order to remove the solvent used in step a), without isolation of the product formed.

[0024] In a specific and preferred embodiment of the invention, the benzyl ester of quinapril is obtained by condensation of the N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine and of the benzyl ester of (S)-1,2,3,4- tetrahydro-3-isoquinolinecarboxylic acid. The resulting benzyl ester of quinapril (II), without isolating, is subjected to the previously described treatment, for example, in patent BE 892.552.

[0025] The following examples serve the purpose of illustrating specific forms of embodiment of the process object of the invention, and they must not be considered as limiting to the scope of the same. All the X-ray diffraction analyses were carried out by the crystalline powder method ($\lambda = 1,5419 \text{ \AA}$), the preparations of the sample were performed on a dry standard.

Material of the anode: copper

Wavelength, $\lambda_1 (\text{\AA}) = 1,54060$

Wavelength, $\lambda_2 (\text{\AA}) = 1,54439$

Initial angle ($2\theta^\circ$) : 6,025

Final angle ($2\theta^\circ$) : 39,9855

Initial d value (\AA) = 14,65735

Final d value (\AA) = 2,25302

EXAMPLE 1

Preparation of the benzyl ester of (S,S,S) 2-[2- [(1-(ethoxycarbonyl)-3-phenylpropyl) amino] 1-oxopropyl] - 1,2,3,4- tetrahydro-3- isoquinolinecarboxylic acid [benzyl ester of quinapril (II)]

[0026] 51.3 g (0.12 moles) of the para-toluenesulfonate of the benzyl ester of (S)-1,2,3,4- tetrahydro - isoquinoline-3- carboxylic acid are suspended in 150 ml of toluene. 200 ml of 10% sodium bicarbonate solution are added under stirring and the mixture is shaken until complete dissolution is achieved. The organic phase is allowed to decant and it is separated, and the same is again washed with 100 ml of 10% sodium bicarbonate solution, and it is subsequently dried with sodium sulphate and filtered. To this toluene based solution, 36.0 g (0.12 moles) of the N-carboxyanhydride of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-L-alanine, dissolved in 75 ml of toluene, are added, at room temperature, in 1 hour. Approximately 4 hours after the addition of said N-carboxyanhydride, the reaction is finished. The toluene phase is washed with a 5% sodium hydroxide solution, followed by water, and the solvent is vacuum-distilled until an oil is

obtained, 62 g (Yield: 98%) which is the benzyl ester of quinapril.

[0027] After forming the maleate, it is characterised by:

- HPLC: the has a purity of 99.3%
- Titration: 100.2%
- $[\alpha]_D^{25} = -12.93^\circ$ (2% methanol)

IR (KBr) (ν , cm^{-1}): 3520, 3050, 2980, 1746, 1656, 1603, 1455, 1347, 1211, 1010, 751, 697.

[0028] In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

[0029] $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) ($\delta(\text{ppm})$): 10,40 (wide band, 3H); 7,40-7,00 (m, 14 H); 6,29 (s, 2H); 5,43 (dd, $J_1 = 3,9$ Hz, $J_2 = 5,9$ Hz, 1H); 5,02 (m, 2H); 4,60 (m, 2H); 4,44 (q, $J_1 = J_2 = J_3 = 7,1$ Hz, 1H); 4,23 (m, 2H); 3,77 (t_{min}), 3,72 (t, $J_1 = 6,3$ Hz, 1H); 3,45 - 3,05 (m, 2H); 2,85 - 2,65 (m, 2H); 2,30 - 2,15 (m, 2H); 1,6 (d_{min} , $J_1 = 6,8$ Hz), 1,45 (d, $J_1 = 6,9$ Hz), 3H; 1,28 (t, $J_1 = J_2 = 7,2$ Hz, 3H).

[0030] $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) ($\delta(\text{ppm})$): 170,4 (min), 170,1, 169,7 (min), 169,2 (min), 169,1, 139,6 (min), 139,5, 135,3, 135,1 (min), 134,5, 131,8, 131,3 (min), 130,9 (min), 130,7, 128,6, 128,5, 128,4, 128,3, 128,1, 128,0, 127,9, 127,8, 127,7, 127,4, 127,3, 126,6, 126,5, 126,4, 126,1, 67,9 (min), 67,2, 62,6, 62,4 (min), 59,5 (min), 58,6, 54,7 (min), 54,5 (min), 53,5, 52,6, 45,2, 44,5 (min), 32,4 (min), 32,1, 31,3 (min), 31,2, 30,5, 16,8 (min), 15,6, 14,0 (min), 13,9.

EXAMPLE 2

Preparation of (S,S,S) 2-[2-[(1-(ethoxycarbonyl)-3-phenylpropyl)amino]1-oxopropyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride [Quinapril hydrochloride (I)]

2.1. Toluene solvate of quinapril hydrochloride.

[0031] 62.0 g of the benzyl ester of quinapril, obtained according to Example 1, are dissolved with 400 ml of ethanol and 10 ml of concentrated hydrochloric acid, 3.1 g of 5% Pd/C (paste) catalyst are added and the mixture is hydrogenated at room temperature and at a pressure 10^5 Pa (1 bar) for 3 hours. After hydrogenation has concluded, the catalyst is filtered, most part of the ethanol is vacuum-distilled and 150 ml of toluene are added. Subsequently, most of the solvent is vacuum-distilled again and another 150 ml of toluene are added. Subsequently it is allowed to stand at room temperature, which leads to the precipitation of a solid which is filtered and dried under a vacuum at 40°C . 58,5 g were obtained (Yield: 88%) of a product which corresponds to the toluene solvate of quinapril hydrochloride.

[0032] IR (KBr) (ν , cm^{-1}): 3520, 3026, 3003, 2928, 2802, 1755, 1742, 1711, 1646, 1558, 1538, 1495, 1455, 1203, 758, 737.

[0033] In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

[0034] $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) ($\delta(\text{ppm})$): 7,20 - 7,00 (m, 14 H); 5,15 (t wide), 4,97 ($width_{\text{min}}$), 1H; 4,82 - 4,45 (m, 3H); 4,35 - 4,05 (m, 2H); 3,90 (t wide, 1H); 3,42 - 3,05 (m, 2H); 2,90 - 2,62 (m, 2H); 2,42 - 2,20 (m, 2H); 2,38 (s, 3H); 1,68 (d, $J_1 = 6,2$ Hz); 1,60 (d_{min} , $J_1 = 6,2$ Hz), 3H; 1,28 (t_{min} , $J_1 = J_2 = 4,0$ Hz); 1,22 (t, $J_1 = J_2 = 4,0$ Hz), 3H.

[0035] $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) ($\delta(\text{ppm})$): 172,2, 171,4 (min), 169,2, 168,6, 168,2 (min), 168,0, 139,6 (min), 139,4, 137,8, 132,2, 131,4, 131,3, 131,2, 129,0, 128,6, 128,4, 128,2, 127,7, 127,1, 126,4, 126,3, 126,2, 125,2, 63,2 (min), 62,9, 59,1 (min), 58,9, 54,9 (min), 54,6 (min), 54,5, 53,1, 45,4, 44,1 (min), 31,9 (min), 31,4, 31,1, 31,0, 30,1 (min), 21,4, 16,2 (min), 15,2, 14,0 (min), 13,9.

2.2. Ethyl formate solvate of quinapril hydrochloride.

[0036] The 58.5 g of toluene solvate are shaken at $40 - 45^\circ\text{C}$ with 234 ml of ethyl formate, for 2 hours, and is subsequently cooled down to a temperature comprised between 20 and 25°C for two additional hours. The resulting product is filtered and dried in a vacuum oven at a temperature of 30°C , for four hours, to obtain 54 g of ethyl formate solvate of quinapril hydrochloride (Yield: 95%).

[0037] IR (KBr) (ν , cm^{-1}): 3520, 3028, 3001, 2979, 2935, 2857, 1744, 1718, 1648, 1546, 1495, 1462, 1454, 1432, 1388, 1260, 1199, 756.

[0038] In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

[0039] $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) ($\delta(\text{ppm})$): 10,00 (s wide, 1H), 8,95 (s wide, 1H), 8,02 (s, 1H); 7,15 (m, 9H); 5,15 ($J_1 = J_2 = 5,6$ Hz), 4,95 ($width_{\text{min}}$), 1H; 4,82 - 4,62 (m, 2H); 4,60 - 4,42 (m, 1H); 4,20 (q, ($J_1 = J_2 = J_3 = 7,0$ Hz, 2H); 4,09 - 3,90 (m, 1H); 3,68 (q_{min}); 3,40 - 3,05 (m, 2H); 2,97 - 2,59 (m, 2H); 2,42 - 2,20 (m, 2H); 1,67 (d, $J_1 = 7,0$ Hz), 1,56 (d_{min}).

$J_1 = 7,0 \text{ Hz}$, 1H), 1,30 (t, $J_1 = J_2 = 7,0 \text{ Hz}$), 1,18 ($J_1 = J_2 = 7,0 \text{ Hz}$), 3H.

[0040] ^{13}C -NMR (CDCl_3 , 75 MHz) ($\delta(\text{ppm})$): 172,2, 171,3 (min), 169,2 (min), 168,6, 168,0, 161,0, 139,7 (min), 139,4, 132,2, 131,4 (min), 131,3 (min), 131,2, 128,5 (min), 128,4, 128,2, 127,2, 127,1, 126,3, 126,2, 126,1, 63,1 (min), 62,9, 59,9, 59,1 (min), 58,9, 58,2 (min), 54,8 (min), 54,6 (min), 54,5, 53,1, 45,4, 44,1 (min), 31,8 (min), 31,3, 31,1, 31,0, 30,8 (min), 30,1, 16,2 (min), 15,2, 14,1, 14,0 (min), 13,9.

X-Ray Diffraction (powder) Ethyl formate solvate of quinapril hydrochloride	
Angle ($2\theta^\circ$)	Relative intensity (%)
8,82	32,7
10,88	23,3
11,47	20,9
12,05	16,5
13,63	34,4
15,89	12,5
16,08	17,2
16,48	27,4
16,85	32,7
18,05	10,4
18,42	17,8
18,68	24,6
19,52	50,7
19,75	33,2
20,11	45,3
21,20	36,6
21,86	100,0
23,07	15,3
23,59	30,1
24,50	42,5
26,66	14,5
27,16	22,7
27,45	10,6
28,34	13,1
28,71	15,6
29,66	29,5
30,56	14,5
34,87	13,5

2.3. Methyl acetate solvate of quinapril hydrochloride

[0041] Following a similar process to that described in Example 2.2., but changing ethyl formate for methyl acetate,

the corresponding methyl acetate solvate of quinapril hydrochloride (Yield: 95%) was obtained, which is characterised by the following spectroscopic data.

[0042] IR (KBr) (ν , cm^{-1}): 3500, 3084, 3003, 2860, 1746, 1735, 1706, 1648, 1545, 1495, 1455, 1259, 1196, 755.

[0043] In solution, this compound is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

[0044] ^1H -NMR (CDCl_3 , 300 MHz) (δ (ppm)): 10,10 (s wide, 1H); 9,10 (s wide, 1H); 7,21 - 7,06 (m, 9H); 5,14 (t, $J_1 = J_2 = 5,6$ Hz, 1H); 4,80 - 4,67 (m, 2H); 4,57 (m, 1H); 4,21 - 4,19 (m, 2H); 4,16 - 3,89 (m, 1H); 3,66 (s, 3H); 3,41 - 3,00 (m, 2H); 2,72 - 2,62 (m, 2H); 2,34 - 2,29 (m, 2H); 2,05 (s, 3H); 1,67 (d, $J_1 = 6,8$ Hz), 1,57 (d_{min} , $J_1 = 6,8$ Hz), 3H; 1,21 (t_{min} , $J_1 = J_2 = 6,9$ Hz); 1,17 (t, $J_1 = J_2 = 6,9$ Hz), 3H.

[0045] ^{13}C -NMR (CDCl_3 , 75 MHz) (δ (ppm)): 172,2, 171,5 (min), 169,2 (min), 168,6, 168,3 (min), 168,1, 139,6 (min), 139,4, 132,2, 131,5 (min), 131,3 (min), 131,2, 128,6, 128,5, 128,4, 128,3 (min), 127,8 (min), 127,2, 126,4, 126,2 (min), 63,2 (min), 62,9, 58,9, 54,7 (min), 54,5, 53,2, 51,5, 45,4, 44,2 (min), 31,9 (min), 31,4, 31,1, 31,0, 30,2 20,6, 16,1 (min), 15,5, 14,0 (min), 13,9.

X-Ray Diffraction (powder) Methyl acetate solvate of quinapril hydrochloride	
Angle ($2\theta^\circ$)	Relative intensity (%)
8,86	26,0
10,95	26,0
11,79	19,2
13,73	45,9
16,18	18,2
16,57	37,7
16,87	60,4
18,76	18,6
18,93	18,6
19,59	33,2
20,16	81,9
20,91	19,2
21,56	30,7
21,93	100,0
22,18	28,7
23,22	14,6
23,65	35,4
24,62	52,6
27,17	34,0
28,51	16,6
28,93	22,9
30,69	21,6
30,85	14,0

- HPLC: 99.8%
- Titration: 100.2%
- $[\alpha]^R = +15.9^\circ$ (2% methanol)

[0048] In solution, quinapril hydrochloride is a mixture of two rotamers. The distribution of the rotamers is observed, in some cases, in the proton and carbon 13 nuclear magnetic resonance (NMR) spectra.

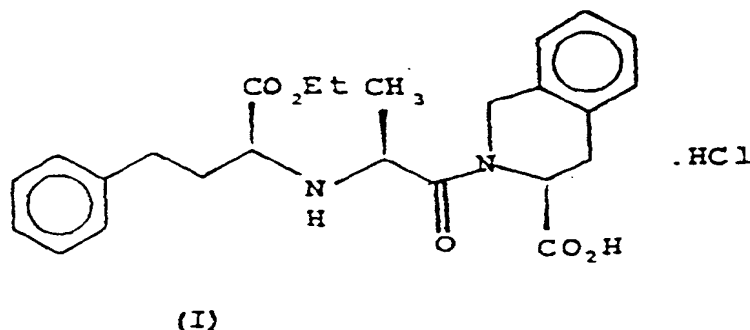
[0049] ¹H-NMR (CDCl₃, 300 MHz) (δ(ppm)): 7,23, (m, 9H); 5,12 (m, 1H); 4,9 - 4,4 (m, 3H); 4,19 (m, 2H); 3,91 (m); 3,79 (m_{min}), 1H; 3,3 - 3,1 (m, 2H); 2,77 - 2,61 (m, 2H); 2,20 (m, 2H); 1,51 (d, J₁ = 6,4 Hz), 1,49 (d_{min}, J₁ = 5,1 Hz), 3H; 1,22 (t_{min}, J₁ = J₂ = 7,3 Hz), 1,17 (t, J₁ = J₂ = 7,3 Hz), 3H.

[0050] ¹³C-NMR (CDCl₃, 75 MHz) (δ(ppm)): 171.5, 171.4, 168.5, 140.2, 132.5, 132.4, 132.1 (min), 131.5 (min), 128.5, 128.4, 128.2, 128.1, 127.1, 126.7, 126.6, 126.3, 126.1, 125.4, 62.2 (min), 62.0, 57.4 (min), 57.3, 53.9 (min), 53.1 (min), 52.7, 52.0, 44.5, 43.6 (min), 31.3 (min), 30.8, 30.6 (min), 30.4, 30.0, 21.1 (min), 16.2 (min), 14.7, 13.9.

X-Ray Diffraction (powder) Quin- april hydrochloride	
Angle (2θ°)	Relative intensity (%)
11,18	31,9
12,17	29,4
17,38	33,9
19,83	37,9
28,34	10,0

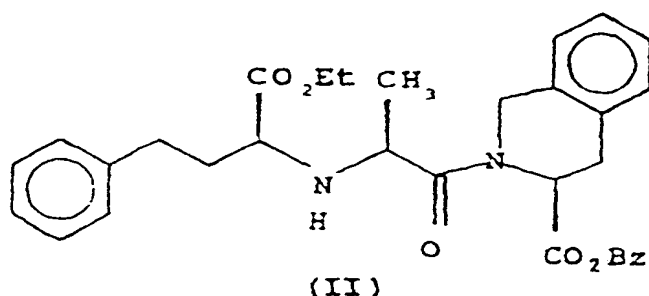
Claims

1. A process for obtaining quinapril hydrochloride of formula (I)



which comprises the stages of:

a) hydrogenolysis of the benzyl ester of quinapril (II)



where Bz is the benzyl radical;

b) removal of the solvent used in step a);

c) addition of toluene to precipitate the quinapril hydrochloride as a toluene solvate;

d) treatment of the toluene solvate of quinapril hydrochloride with a solvent belonging to Class 3, capable of forming a solvate of quinapril hydrochloride from which it is possible to eliminate said solvent by drying in an oven without degrading the quinapril hydrochloride; and

e) drying of the solvate obtained in step d) to yield quinapril hydrochloride (I).

2. A process according to claim 1 wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out in an alcoholic solvent, with treatment with concentrated hydrochloric acid or with a solution of hydrogen chloride in isopropanol, and hydrogenation with hydrogen gas in the presence of a hydrogenation catalyst.

3. A process according to claim 2, wherein said alcoholic solvent is chosen from between ethanol or isopropanol.

4. A process according to claim 2, wherein the hydrogenation is carried out at a pressure comprised between 10^4 Pa and 2×10^5 Pa.

5. A process according to claim 2, wherein the hydrogenation is carried out at a temperature comprised between 10 and 40 °C.

6. A process according to claim 2, wherein the hydrogenation catalyst is Pd/C.

7. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using ethanol as a solvent, concentrated hydrochloric acid, a pressure of 10^5 Pa (1 bar) and room temperature.

8. A process according to claim 2, wherein the hydrogenolysis reaction of the benzyl ester of quinapril (II) is carried out using isopropanol as a solvent, a solution of hydrogen chloride in isopropanol, a pressure of 2×10^5 Pa (2 bar) and a temperature of approximately 30 °C.

9. A process according to claim 2, wherein the molar ratio between the benzyl ester of quinapril (II) and the hydrochloric acid can be equal or slightly greater to the stoichiometric one.

10. A process according to claim 1, wherein the removal of the solvent used in stage a) is carried out by vacuum-distillation.

11. A process according to claim 1, wherein the Class 3 solvent used to treat the toluene solvate of quinapril hydrochloride is chosen from among ethyl formate and methyl acetate.

12. A process according to claim 1, wherein the treatment of the toluene solvate of quinapril hydrochloride with the Class 3 solvent is carried out at a temperature comprised between -10 °C and 45 °C, for a period of time comprised between 1 and 2 hours, and is subsequently cooled down to a temperature comprised between 20 °C and 25 °C, for a period of time comprised between 1 and 2 hours.

13. A process according to claim 1, wherein the Class 3 solvent solvate of quinapril hydrochloride is chosen from

(continued)

X-Ray Diffraction (powder) Ethyl formate solvate of quinapril hydrochloride	
Angle (2 θ)	Relative intensity (%)
24,50	42,5
26,66	14,5
27,16	22,7
27,45	10,6
28,34	13,1
28,71	15,6
29,66	29,5
30,56	14,5
34,87	13,5

20. An ethyl formate solvate of quinapril hydrochloride according to claim 19, characterised in that its infrared spectrum presents the following peaks:

IR (KBr) (ν , cm^{-1}) : 3520, 3028, 3001, 2979, 2935, 2857, 1744, 1718, 1648, 1546, 1495, 1462, 1454, 1432, 1388, 1260, 1199, 756.

21. A methyl acetate solvate of quinapril hydrochloride characterised in that its X-ray diffraction pattern presents the following characteristics:

X-Ray Diffraction (powder) Methyl acetate solvate of quinapril hydrochloride	
Angle (2 θ)	Relative intensity (%)
8,86	26,0
10,95	26,0
11,79	19,2
13,73	45,9
16,18	18,2
16,57	37,7
16,87	60,4
18,76	18,6
18,93	18,6
19,59	33,2
20,16	81,9
20,91	19,2
21,56	30,7
21,93	100,0
22,18	28,7

(continued)

X-Ray Diffraction (powder) Methyl acetate solvate of quinapril hydrochloride	
Angle (2 θ)	Relative Intensity (%)
23,22	14,6
23,65	35,4
24,62	52,6
27,17	34,0
28,51	16,6
28,93	22,9
30,69	21,6
30,85	14,0

22. A methyl acetate solvate of quinapril hydrochloride according to claim 21, characterised in that its infrared spectrum presents the following peaks:

IR (KBr) (ν , cm^{-1}) : 3500, 3084, 3003, 2860, 1746, 1735, 1706, 1648, 1545, 1495, 1455, 1259, 1196, 755.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ES 98/00145

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D 217/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS, CIBEPAT, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4761479 A (GOEL) 2 August 1988 (02.08.88) claim 1	1
A	US 4344949 A (HOEFLE) 17 August 1982 (17.08.82) claims 1, 4 and 10; example 2	1
A	BE 892552 A (USV PHARM. CORPORATION) 20 September 1982 (20.09.82) claim 13	1

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

3 September 1998 (03.09.98)

Date of mailing of the international search report

21 September 1998 (21.09.98)

Name and mailing address of the ISA/

S.P.T.O.

Authorized officer

Facsimile No.

Telephone No.

Form PCT/ISA/2:0 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/ES 98/00145

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4761479 A	02.08.1988	KR 9607087 A EP 285992 A CA 1291999 A AU 605555 A JP 63258459 A	27.05.1996 12.10.1988 12.11.1991 17.01.1991 25.10.1988
US 4344949 A	17.08.1982	ZA 8106332 A FI 881985 A DK 436081 A US 4532342 A SU 1148560 A LU 88321 A HK 43389 A EP 96157 A EP 49605 A CA 1331615 A CA 1331614 A AU 7541681 A AU 5299186 A JP 57088164 A	29.09.1982 27.04.1988 04.04.1982 30.07.1985 30.03.1985 04.05.1994 07.06.1989 21.12.1983 14.04.1982 23.08.1994 23.08.1994 06.05.1982 17.07.1986 12.06.1982
BE 892552 A	20.09.1982	ZA 8201833 A FI 820974 A DK 120982 A IN 156096 A GB 2095252 A FR 2502149 A SE 8201654 A DE 3209708 A CH 658455 A AU 8158482 A NL 8201066 A JP 57165355 A	26.01.1983 20.09.1982 20.09.1982 11.05.1985 29.09.1982 24.09.1982 20.09.1982 21.10.1982 14.11.1986 23.09.1982 18.10.1982 12.10.1982

Form PCT/ISA/210 (patent family annex) (July 1992)